

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 04 April 2001 (04.04.01)	Applicant's or agent's file reference GM/MC/R33-78
International application No. PCT/SG99/00128	Priority date (day/month/year) 02 July 1999 (02.07.99)
International filing date (day/month/year) 17 November 1999 (17.11.99)	
Applicant LIAN-HUI, Zhang et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 16 January 2001 (16.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

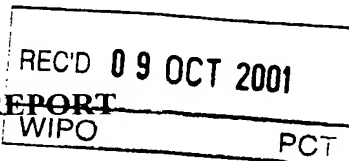
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Zakaria EL KHODARY Telephone No.: (41-22) 338.83.38
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INTERNATIONAL COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 1515 G47/KS/JKS	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/SG99/00128	International Filing Date (<i>day/month/year</i>) 17 November 1999	Priority Date (<i>day/month/year</i>) 2 July 1999
International Patent Classification (IPC) or national classification and IPC Int. Cl.⁷ C12N 15/31; C07K 14/195; A61K 35/74; A61K 38/16		
Applicant INSTITUTE OF MOLECULAR AGROBIOLOGY et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

- | | | |
|------|-------------------------------------|---|
| I | <input checked="" type="checkbox"/> | Basis of the report |
| II | <input type="checkbox"/> | Priority |
| III | <input type="checkbox"/> | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| IV | <input type="checkbox"/> | Lack of unity of invention |
| V | <input checked="" type="checkbox"/> | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| VI | <input type="checkbox"/> | Certain documents cited |
| VII | <input type="checkbox"/> | Certain defects in the international application |
| VIII | <input checked="" type="checkbox"/> | Certain observations on the international application |

Date of submission of the demand 16 January 2001	Date of completion of the report 21 September 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer Gillian Allen TELEPHONE NO. (02) 6283 2266

I. Basis of the report1. With regard to the **elements** of the international application:*

- ☒ the international application as originally filed.
- ☐ the description, pages , as originally filed,
 pages , filed with the demand,
 pages , received on with the letter of
- ☐ the claims, pages , as originally filed,
 pages , as amended (together with any statement) under Article 19,
 pages , filed with the demand,
 pages , received on with the letter of
- ☐ the drawings, pages , as originally filed,
 pages , filed with the demand,
 pages , received on with the letter of
- ☐ the sequence listing part of the description:
 pages , as originally filed
 pages , filed with the demand
 pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 2, 3, 6-18 and 23-25	YES
	Claims 1, 4, 5 and 19-22	NO
Inventive step (IS)	Claims 2 and 6-17	YES
	Claims 1, 3-5, and 18-25	NO
Industrial applicability (IA)	Claims 1-25	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

Citations

- D1 WO 96/29392 A(UNISEARCH LTD) 26/9/96
- D2 WO 98/57618 (UNIVERSITY OF MONTANA RESEARCH AND DEVELOPMENT INSTITUTE) 23/12/98
- D3 US 5 591 872 (THE UNIVERSITY OF IOWA RESEARCH FOUNDATION) 7/1/97
- D4 Luo Z-Q et al. The antiactivator TraM interferes with the autoinducer-dependent binding of the quorum sensing activator TraR to DNA by interacting with the C-terminal region of the protein. Abstracts of the general meeting of the American Society for Microbiology 30 May 1999. 3 June 1999. p H91
- D5. Schaefer AL et al. Quorum sensing in *Vibrio fischeri*: probing autoinducer-LuxR interactions with autoinducer analogues. J Bacteriol. 1996. 178(10): 2897-2901.
- D6 Eberhard A et al. Autoinducer of bioluminescence in *Vibrio fischeri*. Arch Microbiol. 1986. 146(1): 35-40
- D7 Zhu J et al. Analogs of the autoinducer 3-oxooctanyl-homoserine lactone strongly inhibit activity of the TraR protein of *Agrobacterium tumifaciens*. J Bacteriol. 1998. 180(20): 5398-5405.

New Citation

- D8 Hwang I et al. A new regulatory element modulated homoserine lactone-mediated autoinduction of Ti plasmid conjugal transfer. J Bacteriol. 1995. 177(2): 449-458.

Novelty. This objection is maintained from the first opinion

The closest prior art is considered to be that of D8. D8 discloses the nucleotide and amino acid sequences of TraM, which suppresses the homoserine mediated Tra autoactivation system in *Agrobacterium tumifaciens*. It also discloses the gene cloned into an expression vector in *E coli*, and gel isolation of the protein. The nucleotide was identified by screening cosmid clones of *A tumifaciens*, which can be assumed to be from a gene library. It does not appear that the *E coli* strain used inactivated the autoinducer. Claims 1, 4, 5, 19, 20-22 lack novelty over this citation.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The applicant has disclosed only one bacterial autoinducer inactivator, whose nucleic acid and amino acid sequences are given by SEQ ID NOS 1 and 2. Thus it is not considered that the description provides support for any bacterial autoinducer inactivators other than the AiiA protein of the description and its encoding DNA together with close functional homologues thereof. This is particularly so in view of the disclosures of D8 which discloses a bacterial autoinducer inactivator, TraM, that is not a homologue of AiiA. It is therefore considered that claims 13-5, 7, 9-14, 16, 18-25, which are not limited to applicants' disclosed sequences, are not fully supported by the description.

Note

Claims 7-10, 14 and 15 encompass methods for the treatment of animals not excluding humans. There are no unified criteria among the member countries of the PCT as to the patentability of such claims.

Supplemental Box V

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Novelty and Inventive Step

The attorney has argued that the present invention is to a DNA coding for a bacterial DNA autoinducer inactivation protein, and that TraM functions to sequester TraR from interaction with AAI and that it only so functions when overexpressed. However, it is maintained that TraM is a protein capable of causing inactivation of homoserine lactone mediated autoactivation, and as such, falls within the scope of claim 1.

The attorney also argues that the present claims are to an isolated DNA molecule encoding a bacterial autoinducer protein that makes AAI lose its biological activity. However, claim 1 is simply to a bacterial autoinducer inactivation protein. It is not limited to inactivators that affect the biological activity of the AAI protein.

It is pointed out that the lack of novelty and inventive step is due to the fact (see also Box VIII, Certain observations on the international application) that claim 1 is to all or any proteins that inactivate all or any bacterial autoinducers, and is not limited to proteins whose sequences are disclosed in the SEQ ID NOs of the specification, or functional homologues thereof. These are accepted as novel and inventive.

Inventive Step. This objection is maintained from the first opinion.

Claims 1, 4, 5, 19, 20-22 as for novelty

Claims 3, 18 and 23-25 do not contain any features that would confer invention on the claims over the disclosures of D8. Therefore claims 3, 18 and 23-25 are considered to lack inventive step over D8

However, the citation does not suggest the use of TraM to treat bacterial diseases of plants or animals. Moreover, the amino acid sequence of TraM is not homologous to SEQ ID NO 2 of the present application. Therefore claims 2 and 6-17 are considered novel and inventive over the prior art.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GM/MC/R33-78	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. PCT/SG 99/00128	International filing date (day/month/year) 17/11/1999	(Earliest) Priority Date (day/month/year) 02/07/1999
Applicant INSTITUTE OF MOLECULAR AGROBIOLOGY OF.....et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

- ☐ the text is approved as submitted by the applicant.
- ☒ the text has been established by this Authority to read as follows:

**GLOBAL REGULATORS OF BACTERIAL PATHOGENIC GENES; BACTERIAL AUTOINDUCER
INACTIVATION PROTEIN, AS TARGETS FOR ENGINEERING DISEASE RESISTANCE**

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☒ because this figure better characterizes the invention.
- None
☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG 99/00128

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7 to 10, 14 and 15
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PC 99/00128

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/31 C07K14/195 A61K35/74 A61K38/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 29392 A (UNISEARCH LTD ;KJELLEBERG STAFFAN (AU); STEINBERG PETER (AU); NYS) 26 September 1996 (1996-09-26) the whole document ---	1,3-5,7, 9-14,16, 18-22
Y	WO 98 57618 A (UNIV MONTANA RES DEV INST ;DAVIES DAVID G (US); COSTERTON JOHN WIL) 23 December 1998 (1998-12-23) the whole document ---	1,3-5,7, 9-14,16, 18-22
Y	US 5 591 872 A (PEARSON JAMES P ET AL) 7 January 1997 (1997-01-07) the whole document --- -/--	1,3-5,7, 9-14,16, 18-22

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

4 Apr11 2000

Date of mailing of the international search report

12/04/2000

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
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Authorized officer

H1x, R

INTERNATIONAL SEARCH REPORT

International Application No

PC 99/00128

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>LUO Z -Q ET AL: "THE ANTIACTIVATOR TraM INTERFERES WITH THE AUTOINDUCER-DEPENDENT BINDING OF THE QUORUM-SENSING ACTIVATOR TraR TO DNA BY INTERACTING WITH THE C-TERMINAL REGION OF THE PROTEIN" ABSTRACTS OF THE GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, 30 May 1999 (1999-05-30) - 3 June 1999 (1999-06-03), page H91 XP000884164 abstract</p>	1,3-5,7, 9-14,16, 18-22
Y	<p>--- SCHAEFER A L ET AL: "QUORUM SENSING IN VIBRIO FISCHERI: PROBING AUTOINDUCER-LuxR INTERACTIONS WITH AUTOINDUCER ANALOGS" JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 178, no. 10, May 1996 (1996-05), pages 2897-2901, XP000884120 ISSN: 0021-9193 the whole document</p>	1,3-5,7, 9-14,16, 18-22
Y	<p>--- EBERHARD A ET AL: "ANALOGS OF THE AUTOINDUCER OF BIOLUMINESCENCE IN VIBRIO FISCHERI" ARCHIVES OF MICROBIOLOGY, vol. 146, no. 1, October 1986 (1986-10), pages 35-40, XP000884126 ISSN: 0302-8933 the whole document</p>	1,3-5,7, 9-14,16, 18-22
Y	<p>--- ZHU J ET AL: "ANALOGS OF THE AUTOINDUCER 3-OXOOCTANOYL-HOMOSERINE LACTONE STRONGLY INHIBIT ACTIVITY OF THE TraR PROTEIN OF AGROBACTERIUM TUMEFACIENS" JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 180, no. 20, October 1998 (1998-10), pages 5398-5405, XP000884118 ISSN: 0021-9193 the whole document</p>	1,3-5,7, 9-14,16, 18-22
A	<p>--- SLOCK J ET AL: "CRITICAL REGIONS OF THE VIBRIO FISCHERI LuxR PROTEIN DEFINED BY MUTATIONAL ANALYSIS" JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 172, no. 7, July 1990 (1990-07), pages 3974-3979, XP000884181 ISSN: 0021-9193 the whole document</p> <p style="text-align: center;">--- -/--</p>	

INTERNATIONAL SEARCH REPORT

International Application No

PC 99/00128

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>POELLINGER K A ET AL: "INTRAGENIC SUPPRESSION OF A LuxR MUTATION: CHARACTERIZATION OF AN AUTOINDUCER-INDEPENDENT LuxR" FEMS MICROBIOLOGY LETTERS,NL,AMSTERDAM, vol. 129, no. 1, 1995, pages 97-102, XP000884123 ISSN: 0378-1097 the whole document</p>	
A	<p>REVERCHON S ET AL: "INTEGRATION OF THE QUORUM-SENSING SYSTEM IN THE REGULATORY NETWORKS CONTROLLING VIRULENCE FACTOR SYNTHESIS IN ERWINIA CHRYSANTHEMI" MOLECULAR MICROBIOLOGY,GB,BLACKWELL SCIENTIFIC, OXFORD, vol. 29, no. 6, September 1998 (1998-09), pages 1407-1418, XP000884219 ISSN: 0950-382X the whole document</p>	
A	<p>CHOI S H ET AL: "THE C-TERMINAL REGION OF THE VIBRIO FISCHERI LuxR PROTEIN CONTAINS AN INDUCER-INDEPENDENT lux GENE ACTIVATING DOMAIN" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 88, December 1991 (1991-12), pages 11115-11119, XP000876990 ISSN: 0027-8424 cited in the application the whole document</p>	
A	<p>HANZELKA B L ET AL: "EVIDENCE THAT THE N-TERMINAL REGION OF THE VIBRIO FISCHERI LuxR PROTEIN CONSTITUTES AN AUTOINDUCER-BINDING DOMAIN" JOURNAL OF BACTERIOLOGY,US,WASHINGTON, DC, vol. 177, no. 3, February 1995 (1995-02), pages 815-817, XP000884175 ISSN: 0021-9193 cited in the application the whole document</p>	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC 99/00128

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9629392 A	26-09-1996	AU 708962 B	19-08-1999
		AU 4999696 A	08-10-1996
		BR 9607661 A	16-06-1998
		CA 2215797 A	26-09-1996
		CN 1185173 A	17-06-1998
		EP 0815201 A	07-01-1998
		JP 11502108 T	23-02-1999
		NZ 303630 A	26-01-1998
WO 9857618 A	23-12-1998	AU 7977698 A	04-01-1999
		AU 8258998 A	04-01-1999
		WO 9858075 A	23-12-1998
US 5591872 A	07-01-1997	NONE	